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SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
07/909,379	07/06/92	SCHMITT-WILLICH	H SCH-1199
			EXAMINER CHAPMAN, A
22M2/1027			
MILLEN, WHITE, ZELANO & BRANIGAN, P. C. ARLINGTON COURTHOUSE PLAZA 1, STE. 1400 2200 CLARENDON BLVD. ARLINGTON, VA 22201			
		ART UNIT	PAPER NUMBER
		2203	13

DATE MAILED: 10/27/93

This is a communication from the examiner in charge of your application.  
COMMISSIONER OF PATENTS AND TRADEMARKS

☐ This application has been examined ☒ Responsive to communication filed on 8/2/93 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), days from the date of this letter.  
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

- |                                                                                         |                                                                                  |
|-----------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| 1. <input checked="" type="checkbox"/> Notice of References Cited by Examiner, PTO-892. | 2. <input checked="" type="checkbox"/> Notice re Patent Drawing, PTO-948.        |
| 3. <input checked="" type="checkbox"/> Notice of Art Cited by Applicant, PTO-1449.      | 4. <input type="checkbox"/> Notice of Informal Patent Application, Form PTO-152. |
| 5. <input type="checkbox"/> Information on How to Effect Drawing Changes, PTO-1474.     | 6. <input type="checkbox"/>                                                      |

Part II SUMMARY OF ACTION

1. ☒ Claims 1-32 are pending in the application.

Of the above, claims 11-16 are withdrawn from consideration.

2. ☐ Claims have been cancelled.

3. ☐ Claims are allowed.

4. ☒ Claims 1-10, 17-32 are rejected.

5. ☐ Claims are objected to.

6. ☐ Claims are subject to restriction or election requirement.

7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.

8. ☐ Formal drawings are required in response to this Office action.

9. ☐ The corrected or substitute drawings have been received on Under 37 C.F.R. 1.84 these drawings are ☐ acceptable, ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).

10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on has (have) been ☐ approved by the examiner, ☐ disapproved by the examiner (see explanation).

11. ☐ The proposed drawing correction, filed on has been ☐ approved, ☐ disapproved (see explanation).

12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received  
☐ been filed in parent application, serial no. ; filed on

13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

14. ☐ Other

EXAMINER'S ACTION

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1. The amendment filed 8/2/93 has been entered. The arguments filed 8/2/93 have been carefully considered and have been found persuasive. Thus, the previous rejections made under 35 U.S.C. 102 and 103 have been withdrawn.

2. Claim 1 is objected to because of the following typographical error:

In line 24 of this claim -(O)<sub>4</sub>-R should be -(O)<sub>r</sub>-R

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

"A person shall be entitled to a patent unless -

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent."

4. The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

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5. Claims 1-3, 6-8, 17-18, 22, and 27-28 are rejected under 35 U.S.C. § 102 (a) as being anticipated Gansow (U.S. Pat. No. 4,824,986).

Applicant's claims include DTPA derivatives wherein the Z substituents may be H or alkyl (when m, q, k, n, l, and r are all 0). Gansow teaches DTPA derivatives with various side chains. In column 3, lines 67-68 Gansow states "Preferred side chains include straight chain alkanes, benzyl, and phenylethylene." Thus, Gansow teaches Applicant's claimed compounds whenever one of the pendant Z groups is a straight chain alkane.

6. Claims 1-10 and 17-32 are rejected under 35 U.S.C. 103 as being unpatentable over Berg et al. (U.S. Pat. No. 5,198,208 or EP 299,795) in view of either Gansow (U.S. Pat. No. 4,824,986) or Gries et al. (EP 263,059).

7. Berg et al. discloses DTPA derivatives "particularly useful for the preparations of diagnostic and therapeutic agents for magnetic resonance imaging, scintigraphy, ultrasound imaging, radiotherapy and heavy metal detoxification" (Abstract). The compounds of the Berg et al. invention contain pendant groups designated R<sub>1</sub> which correspond to Applicant's Z substituents. Applicant's attention is drawn to the compounds listed in columns 14-16 and particularly to the structure IK in column 16. Berg et al. teach in the Abstract that R<sub>1</sub> may be a hydrogen atom, a hydroxyalkyl group, or an optionally hydroxylated alkoxy or alkyloxy group. In column 3, lines 39-50, Berg et al. discusses the metal ions to which the chelate can complex: "It is...particularly preferred that the number of the ion-forming groups X in the compounds of formula I be chosen to equal the valency of the metal species to be chelated by the compound of formula I. Thus, for

example, where Gd(III): is to be chelated, the chelating agent of formula I preferably contains three ion-forming X groups...." Although Berg et al. disclose pendant alkyloxy substituents, they do not mention benzoxy substituents such that a benzyl group would be substituted for an pendant alkyl group of their invention.

Gansow discloses metal chelate protein conjugates useful for tumor imaging and therapy. In column 3, lines 13-33 Gansow teaches that any of the art recognized chelates such as EDTA, DOTA, or DTPA may be used in the invention. In the following paragraph Gansow addresses substitutions on these chelates, and in the very last sentence Gansow states "Preferred side chains include straight chain alkanes, benzyl, and phenylethylene." Metals disclosed in this invention include "Any suitable metal...including metals which exhibit paramagnetism, metal which are fluorescent, and metals which are radioactive. Representative paramagnetic metals include gadolinium..." (col. 5, lines 15-17). Substituting benzyl groups for the alkyl groups of Berg et al. would have been obvious to a person of ordinary skill in the art since Gansow teaches benzyl side chains on DTPA-Gd complexes for use in diagnostic imaging and cancer therapy and because Gansow discloses the equivalence of alkyl and benzyl side chains on DTPA-type ligands.

Similarly, Gries et al. also disclose DTPA derivatives with pendant R<sup>1</sup> groups which correspond to Applicant's Z substituents. Applicant's attention is directed to Formula I and the Abstract. Gries et al. teaches in the Abstract that R<sup>1</sup> can be alkyl groups, phenyl groups, and benzyl groups. Possible metals to which the ligands of Gries et al. can complex are discussed on page 2 and include metals with atomic numbers of 21-29, 31, 32, 38, 39, 42-44, 49, and 57-83 which are useful for diagnostic purposes. Thus, since Gries et al. and Berg et al. both teach DTPA derivatives which complex with Gd and

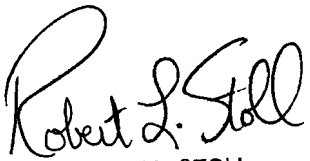
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which are used for diagnosis, it would have been obvious to a person of ordinary skill in the art to modify the invention of Berg et al. by substituting a benzyl group for an alkyl group in the ligand's side chain. Also, since Gries et al. teach the equivalence of alkyl and benzyl groups as side chains, it would be readily obvious that the substitution could be made in order to obtain a DTPA derivative with a pendant benzyloxy group.

8. Applicant's arguments filed 8/2/93 with regard to the Berg et al. reference have been considered but are deemed moot in view of the new grounds of rejection.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Lara Chapman whose telephone number is (703) 308-0450. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0511.

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ROBERT L. STOLL  
SUPERVISORY PRIMARY EXAMINER  
ART UNIT 223